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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/602,325	CHAPLIN ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 15-53* is/are pending in the application.

4a) Of the above claim(s) *5,16,19,22,27,28 and 33-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,15,17,18,20,21,23-26 and 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, without traverse, with the Group I along with combretastatin, nitroglycerin and neoplastic disease/cancer as the elected species is acknowledged. Claims 1-4, 6, 7-8, 15, 17, 18, 20-21, 23-26 and 29-32 read on the elected invention.

Claims 5, 16, 19, 22, 27-28 and 33-53 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claims.

2. With respect to the examiner's election of species requirement, upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Specification

3. The specification mistakenly identifies "propanolol" or "propanolol hydrochloride" as the art-recognized name for Inderal®, 1-[isopropylamino]-3-[1-napthyloxyl]-2-propanol or 1-[isopropylamino]-3-[1-napthyloxyl]-2-propanol hydrochloride (see page 5, line 6; page 10, line 12 and line 23; page 16, line 21, 24 and 29; page 17, line 2 and 26; page 18, line 14, 20 and 26; and page 19, line 3, 30 and 32). The correct generic name for Inderal® or 1-[isopropylamino]-3-[1-napthyloxyl]-2-propanol hydrochloride is "propranolol" or "propranolol hydrochloride. Applicant is requested to make appropriate corrections.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4, 6, 7-8, 15, 17, 18, 20-21, 23-26 and 29-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "treating a cardio toxicity or hypertension induced by a vascular targeting agent selected from the group consisting of a combretastatin, a combretastatin A-4 phosphate, a combretastatin A-1 diphosphate and a pharmaceutically acceptable salt thereof" with the administration of said vascular targeting agent in combination with the specific beta-blocker or vasodilator (e.g., nitroglycerin and propranolol), does not reasonably provide enablement for "a treatment of a disease associated with vascular targeting", "vascular targeting agent", "an anti-hypertensive agent", "a combretastatin analog" and "neoplastic disease". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the

presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant claims are drawn to a method for treating a disease state associated with vascular targeting comprising administration of vascular targeting agent and an anti-hypertensive agent to mammal.

The specification defines the term "vascular targeting" as "the selective destruction, damage or occlusion, whether reversible or irreversible, partial or incomplete, of existing or established microvessels"; "vascular proliferative disorders" as "any mammalian disease state in which the pathology of the disease is characterized by the presence of endothelium, arteries, blood vessels, or neovasculature formed by undesirable and pathological angiogenesis that is associated with disease states other than malignant diseases such as cancer, including without limitation ocular diseases such as wet or age-related macular degeneration, diabetic neovascularization, and other diseases states including psoriasis, rheumatoid arthritis, atheroma, restenosis, Kaposi's sarcoma, haemangioma, and in general, inflammatory diseases characterized by vascular proliferation"; and "neoplastic diseases" as "the abnormal presence of cells which exhibit relatively autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of cell proliferation control" (page 10, line 12 through page 11, line 13).

With respect to the scope of enablement for treating "a disease state associated with vascular targeting" or "a neoplastic disease",

There are no known compounds of similar structure which have been demonstrated to treat all types of "a disease state associated with vascular targeting" or "neoplastic diseases". Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. For example, the existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different method of growth and harm the body. Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against "a disease state associated with vascular targeting" or "neoplastic diseases".

The relative skill of those in the art of pharmaceuticals and unpredictability in the pharmaceutical art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the pharmaceutical utility of the instant compounds encompassed by the instant invention. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The instant claims embrace treatment of any mammalian disease state in which the pathology of the disease characterized by the presence of endothelium, arteries, blood vessels or neovasculature formed by undesirable and pathological angiogenesis that is associated with disease states other than malignant diseases such as cancer, including macular degeneration, diabetic retinopathy, retinopathy of prematurity, diabetic molecular edema, uveitis, and corneal revascularization, psoriasis, rheumatoid arthritis, atheroma, restenosis, Kaposi's sarcoma, haemaniogma and etc... .

The specification discloses the (in vivo) study showing the activity of sodium nitroprusside or propranolol in controlling blood pressure or cardiotoxicity induced by combretastatin disodium phosphate (Examples).

As discussed in preceding comments, although the specification provides enabling disclosure for "treating a cardiotoxicity or hypertension induced by a vascular targeting agent selected from the group consisting of a combretastatin, a combretastatin A-4 phosphate, a combretastatin A-1 diphosphate and a pharmaceutically acceptable salt thereof" with the administration of said vascular targeting agent in combination with the specific beta-blocker or vasodilator (e.g., nitroglycerin and propranolol), none of the specification provides enabling disclosure for the claimed therapeutic treatment of "a disease state associated with vascular targeting" or "a neoplastic disease". There is no demonstrated correlation that the tests and results apply to all of the disorders embraced by the instant claims.

As discussed above, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art, the limited number of examples, and the insufficient amount of guidance present in the specification, one of ordinary skill in the art

would be burdened with undue "painstaking experimentation study" to practice the invention commensurate in scope with these claims (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

With respect to enable of "vascular targeting agent", "an anti-hypertensive agent" or "a combretastatin analog",

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5(BDAI

1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 9999 F.2d 1577, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of treating "a disease state associated with vascular targeting' prior to filling of the instant invention was an unpredictable art.

The claims are very broad due to the vast number of possible compounds of that are described as being "vascular targeting agent", "an anti-hypertensive agent" or "a combretastatin analog". The instant claims cover "vascular targeting agent", "an anti-hypertensive agent" or "a combretastatin analog" that are known to exist and those that may be discovered in the future, for which there is no enablement provided.

Although the specification discloses combretastatin or combretastatin analog, preferably combretastatin A-4-disodium phosphate, as suitable vascular targeting agent and beta-blocker such as propranolol or vasodilator such as sodium nitroprusside dehydrate, the specification fails to provide how to make/screen without "vascular targeting agent", "an anti-hypertensive agent" or "a combretastatin analog" without undue amount of experimentation. As discussed in preceding comments, in the instant case, only a limited number of examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The instant claims read on any compounds having "vascular targeting agent", "an anti-hypertensive agent" or "a combretastatin analog", necessitating an exhaustive search for the embodiments suitable to practice the claimed

invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fishcher, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575.

As discussed above, considering above factors, especially the "sufficient working examples", "the level of skill in the art", "the relative skill and the unpredictability in the pharmaceutical art", "breadth of the claims" and "the chemical nature of the invention", one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds for the claimed methods of prevention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4, 6, 15, 17, 18, 20-21, 23-26 and 29-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding independent claim 1, the phrases "an effective amount" renders the claim indefinite because the claim includes elements not actually disclosed which could mean the administering of the compound is for any therapy, thereby rendering the scope of the claim unascertainable. See MPEP 2173.05(d). The "treatment of a disease state associated with vascular targeting" in the preamble of claim 1 may be implied as being what is meant for "an effective amount" but this is implied at best. An implied limitation is not clear and concise as required under 112, second paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-4, 6, 7-8, 17, 26 and 29-31 are rejected under 35 U.S.C. 102(a) or (e) as being anticipated by Curwen et al. (WO 01/74360 or its English equivalent of PGPub US 2003/0144298 A1).

The claims read on a method of treating a disease state associated with vascular targeting, namely cancer, comprising the administration of an effective amount of vascular targeting agent,

namely combretastatin and an anti-hypertensive agent, namely nitroglycerin, to a mammal (claims 1-4, 6, 17 and 26); and a composition or kit comprising said vascular targeting agent, said anti-hypertensive agent and a pharmaceutically acceptable carrier or diluent, in a container when said composition is formulated into kit (claims 7-8). Further limitations include "said anti-hypertensive agent is administered simultaneously with said vascular targeting agent" (claim 29); "said anti-hypertensive agent is administered prior to the administration of said vascular targeting agent" (claim 30); and "said anti-hypertensive agent is administered following the administration of said vascular targeting agent" (claim 31).

Curwen teaches a pharmaceutical composition or kit comprising a combination of antihypertensive agent (i.e., vasodilator such as nitroglycerine and beta-blocker such as acebutolol, atenolol, propranolol and etc...) antiangiogenic agent such as vascular targeting agent (i.e., combretastatin A4 or N-acetylcolchinol-O-phosphate) that is useful for the treatment of disease state associated with angiogenesis including cancer in a warm-blooded mammal including human, wherein said combination is administered sequentially or simultaneously, when administered sequentially either the antiangiogenic agent or the anti-hypertensive agent is administered first (abstract; [0002], [0019]-[0030], [0052]-[0053], [0057], line 28 of [0060], [0077] and claims 1, 7-9 and 12-14).

Although Curwen is silent about the intended use of said combination for the treatment of a disease state associated with vascular targeting, such property or characteristic deems to be inherent to the referenced method since the referenced treatment of cancer "metes and bounds" the instantly claimed "a disease state associated with vascular targeting". Thus, Curwen anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 15, 18, 20-21, 23-25 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curwen et al. (either WO 01/74360 or its English equivalent of PGPub US 2003/0144298 A1) and further in view of Pettit (WO 99/35150) and Pero (US 6773702).

The teaching of Curwen has been discussed in above 35 USC 102(a) or (e) rejection. However, Curwen does not specifically disclose the limitations of "said pharmaceutically acceptable salt is a sodium salt or a triethylamine salt" (claim 15),"said vascular targeting agent is combretastatin A-4-disodium phosphate" (claim 18), "said combretastatin, combretastatin analog, and a pharmaceutically acceptable salt thereof, is administered at a dosage of 100mg/kg or less" (claim 24), "said vascular targeting agent is administered intravenously" (claim 25) and "said vascular targeting agent is being chronically administered to said animal" (claim 32).

Both Pettit and Pero (WO'150 and US'702) are being provided as a supplemental reference to demonstrate combretastatin A-4 disodium phosphate as known combretastatin A-4 analog having better antineoplastic property (due to improved solubility); and dosage levels of said combretastatin A or combretastatin 4 analog in intravenous 0.1 to about 20 mg/kg and intramuscular 1 to about 50 mg/kg or less (abstract; page 1, lines 4-7; page 35, lines 3-6; amended claims of WO'150 and column 1, lines 14-17, column 5, lines 11-40 and column 9, line 54 of USP'702).

Although the instant claims use the different names for the said ingredients than those taught in the cited references, these references are particularly pertinent and relevant because all the claimed species and their roles are well taught in the cited reference. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities, and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to chronic administration of said vascular targeting agent, such time period will not support the patentability of subject matter encompassed by the prior art unless there is

evidence indicating such time period is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or treatment frequency (or duration) by routine experimentation.

Conclusion

8. No Claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
Primary Patent Examiner
AU 1614